The Applicants respectfully submit that claim 1, as proposed to be amended, no longer refers to polypeptides that comprise fragments or variants of the SEQ ID NO:1 motif, other than the SEQ ID NO:1 motif itself. Claims 43, 46, and 47 have been canceled. Therefore, the Examiner's rejection of claims 1, 43, 44, 45, 46, and 47 with respect to the enablement of peptides comprising a fragment of SEQ ID NO:1 (i.e. at least six consecutive amino acids of the SEQ ID NO:1 motif), or a variant of SEQ ID NO:1 (i.e. wherein the side chains of one or two of the amino acids of SEQ ID NO:1 are altered) is addressed and rendered moot.

Claim 1 as amended is directed to a polypeptide that comprises the motif RMFPNAPYL (SEQ ID NO:1) and includes all such polypeptides that have "at least 8 but fewer than 100 amino acids".

The applicants submit that, even if the longer molecules encompassed by this claim language did not themselves bind to HLA-A0201, they are still capable of being processed by antigen-presenting cells (APCs) **to produce a fragment that binds** to HLA-A0201. The Examiner has rejected claim 1 on the grounds that while larger peptides "are processed to produce smaller peptides that bind MHC class I molecules, the instant specification provides insufficient guidance and direction regarding *which* larger peptides will be recognized by the proteosome and processed to a peptide consisting of SEQ ID NO:1... it would require undue experimentation for one skilled in the art to predict which of the peptides encompassed by the instant claims, other than a polypeptide consisting of SEQ ID NO:1, has the ability to bind MHC class I molecules". The Examiner further asserts that one of ordinary skill in the art would not know how to predict which peptides comprising SEQ ID NO:1 would contain the necessary

recognition site for degradation by the proteasome in view of the Janeway reference's teaching of proteasome subunits dictating specificity. The Applicants respectfully submit that a person of skill in the art would have a hard time finding a polypeptide that comprises the SEQ ID NO:1 motif that **did not** have the ability to be degraded by an APC to produce a peptide that binds to HLA-A0201. Evidence in support of this statement is discussed in Janeway. The passage of Janeway referred to by the Examiner is, presumably, the sentence that bridges pages 125 and 126, namely:

> "The replacement of the constitutive components [of the proteasome] by the interferon-inducible counterparts seems to change the specificity of the proteasome: in interferon-treated cells, there is **increased cleavage of polypeptides after hydrophobic and basic residues**, and reduced cleavage after acidic residues" (**emphasis** added).

It would be readily apparent to one of ordinary skill that, despite the shift in specificity, the interferon-induced proteasome alluded to in Janeway nevertheless maintains a very broad range of action, namely, "increased cleavage of polypeptides after hydrophobic and basic residues". The Applicants respectfully submit that the SEQ ID NO:1 motif ends in a leucine residue. Leucine is a hydrophobic residue. Evidence of this is provided by an extract from The New Oxford English Dictionary (Oxford University Press, 2001) which defines leucine as "a hydrophobic amino acid". Therefore, in view of the Janeway reference, the proteasome would cleave any polypeptide that contains the SEQ ID NO:1 motif, directly after the final residue of the motif (i.e. after the leucine), thereby providing a peptide fragment with a C-terminal portion that ends in the SEQ ID NO:1 motif.

N-terminal trimming of polypeptides is known to occur independently of the proteasome. The Examiner is respectfully referred to the enclosed journal reference by Shastri et al. (Annual Review of Immunology, 2002, 20: 469-493), and in particular to page 479, lines 14-15, which states, "[S]everal lines of evidence indicate that the proteasome is required to generate the C **but not the N terminus** of the final peptide" (**emphasis** added). The Applicants submit that current evidence suggests that N-terminal trimming of peptide fragments occurs within the endoplasmic reticulum of an APC. This is the site where a C-terminal trimmed peptide binds to an MHC class I molecule. The protruding N-terminal is then trimmed back by an aminopeptidase to produce a molecule that is of the 'correct' size to best fit the MHC's peptide binding groove. Again, this is reported in Shastri (at page 483, lines 16-17):

"these studies provide compelling arguments for aminopeptidase trimming in the ER as a key event in the antigen processing pathway".

Thus a peptide containing the SEQ ID NO:1 motif will be cleaved by the proteasome to produce a 'partial' fragment whose C-terminal ends with that motif (but has an extended N-terminal sequence). The peptide will then be transported to the endoplasmic reticulum and bound, at the SEQ ID NO:1 motif, by an MHC class I molecule (i.e. HLA-A0201). This binding will determine the N-terminal trimming of the molecule by aminopeptidases in the endoplasmic reticulum, to produce an antigenic fragment containing the motif of SEQ ID NO:1 that correctly binds to HLA-A0201 for antigen presentation.

The Applicants submit that the identity of the sequences that flank the SEQ ID NO:1 motif is not important to the correct processing of the polypeptide. An APC is able to correctly

process virtually all proteins it is exposed to. This makes absolute sense, since an immune system that is incapable of dealing with new or previously "unseen" proteins would be a poor system indeed. This is stressed in the opening passages of Shastri (page 463, lines 5-10 of the first paragraph under the heading "The peptide/MHC Class I Display"), wherein it is stated, "[B]ecause cells cannot distinguish their normal proteins from non-self or mutant proteins, **they constitutively display peptides derived from all proteins**. For effective immune surveillance it is essential that the major histocompatibility complex (MHC) class I (MHC I) molecules display as large a peptide repertoire as possible to include those originating from novel genes" (**emphasis** added).

Therefore, the Applicants submit that one of ordinary skill would be quite capable without the need for undue experimentation, of producing many different types of polypeptides that would be able to be processed by an APC to produce a peptide having the sequence of the SEQ ID NO:1 motif (and thus binding to HLA-A0201). Rather, the skilled person would only face difficulty in finding peptides that **did not** have this ability. If such a polypeptide were found, the skilled person would consider himself extremely unlucky, but would have no difficulty in choosing alternative polypeptides that were capable of being correctly processed by an APC.

Claims 43-48 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, claim 1, from which claims 44 and 45 depend, no longer refers to polypeptides that comprise fragments or variants of the SEQ ID NO:1 motif. Claim 1, as amended, only refers to a peptide comprising the SEQ ID NO:1 motif itself. The Applicants submit that the claimed peptides are clearly enabled in view of the foregoing discussion. Claims 43 and 46-48 have been canceled.

Claims 1, 4-6, 15 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner has rejected claims 1, 4-6, 15 and 19 on the basis that "there is insufficient written description for a peptide able to bind class I molecules which comprises at least 6 consecutive residues of SEQ ID NO;1, or which comprises at least 6 consecutive residues of SEQ ID NO:1, wherein 2 of said 6 amino acids can be changed." The claims have been amended to delete references to "a peptide comprising at least six consecutive amino acids of SEQ ID NO:1, and variants thereof wherein the side chains of one or two to the amino acids of SEQ ID NO:1 are altered", thereby rendering the Examiner's rejection moot.

Claims 43-48 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner asserts that the instant disclosure of a peptide comprising the amino acid sequence of SEQ ID NO:1 does not adequately describe the scope of the claimed genus. This rejection appears to be directed to claim 1. The term "comprising" in the instant claims does not refer to an *indeterminate* number and type of amino acids. Claim 1 is directed to a peptide having at least 9 but fewer than 100 amino acids, thereby defining the number of amino acids of the peptide. Furthermore, as described above, the *identity* of the sequences that flank the SEQ ID NO:1 motif is not important to the correct processing of the polypeptide. An APC is able to correctly process virtually all proteins it is exposed to. Again, in view of the Janeway publication, the Applicants have submitted that current evidence suggests that N-terminal trimming of peptide fragments occurs within the endoplasmic reticulum of an APC. This is the site where a C-terminal trimmed peptide binds to an MHC class I molecule. The protruding N-terminal is then trimmed back by an aminopeptidase to produce a molecule that is of the 'correct' size to best fit the MHC's peptide binding groove (see enclosed Shastri reference, at page 483, lines 16-17):

"these studies provide compelling arguments for aminopeptidase trimming in the ER as a key event in the antigen processing pathway".

In view of the foregoing discussion, as it relates to claim 1, dependent claims 44 and 45 find more than adequate support in the specification as originally filed, in combination with what is generally known in the art.

Allowance of claims 1, 4, 5, 7, 15, 44 and 45 is respectfully solicited.

Respectfully submitted,

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Date: August 20, 2002

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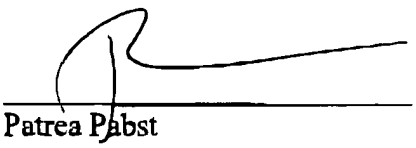

Patrea Pabst

Date: August 20, 2002

U.S.S.N. 09/625,963
Filed: July 26, 2000
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A peptide having at least [8] 9 but fewer than 100 amino acids, which peptide comprises [an] the amino acid sequence [selected from the group consisting of] RMFPNAPYL (SEQ ID NO:1)[; a peptide comprising at least six consecutive amino acids of SEQ ID NO:1, and variants thereof wherein the side chains of one or two to the amino acids of SEQ ID NO:1 are altered].

4. A peptide according to claim 1 wherein the peptide is capable of binding to HLA-A0201.

5. A peptide according to claim 4 wherein when bound to HLA-A0201 the peptide-bound HLA-A0201 is capable of eliciting the production of a cytotoxic T lymphocyte (CTL) which recognises a cell which aberrantly expresses a polypeptide comprising the given amino acid sequence.

Please cancel claim 6.

7. (Twice Amended) A peptide consisting of the amino acid sequence RMFPNAPYL (SEQ ID NO:1).

15. (Twice Amended) A pharmaceutical composition comprising the peptide of Claim 1 and a pharmaceutically acceptable carrier.

Please cancel claim 19.

44. (Amended) The peptide of claim 1 consisting of from [8] 9 to 12 amino acids.

Please cancel claim 43.

45. The peptide of claim 1 which is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind to HLA-A0201.

Please cancel claims 46-48.